Metabolic oxidation regulates embryonic stem cell differentiation.

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Public Summary:
Metabolites offer an important unexplored complementary approach to understanding the pluripotency of stem cells. Using MS-based metabolomics, we show that embryonic stem cells are characterized by abundant metabolites with highly unsaturated structures whose levels decrease upon differentiation. By monitoring the reduced and oxidized glutathione ratio as well as ascorbic acid levels, we demonstrate that the stem cell redox status is regulated during differentiation. On the basis of the oxidative biochemistry of the unsaturated metabolites, we experimentally manipulated specific pathways in embryonic stem cells while monitoring the effects on differentiation. Inhibition of the eicosanoid signaling pathway promoted pluripotency and maintained levels of unsaturated fatty acids. In contrast, downstream oxidized metabolites (for example, neuroprotectin D1) and substrates of pro-oxidative reactions (for example, acyl-carnitines), promoted neuronal and cardiac differentiation. We postulate that the highly unsaturated metabolome sustained by stem cells allows them to differentiate in response to in vivo oxidative processes such as inflammation.

Scientific Abstract:
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